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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,381	DELFOURNE ET AL.	
	Examiner	Art Unit	
	Janet L. Coppins	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5,7-11,13 and 14* is/are allowed.

6)☒ Claim(s) *12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JLC

DETAILED ACTION

Claims 1-5 and 7-14 pending in the instant application.

Response to Amendment

1. Receipt is acknowledged of Applicants' After Final Response, submitted March 14, 2005, which has been reviewed by the Examiner and entered in the file.

2. Accordingly, Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

3. In view of Applicants' persuasive arguments, and the interview with Applicants' attorney of March 9, 2005, the Examiner withdraws the *35 USC § 102* rejections of claims 7-10.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 12 rejected under 35 USC 112, first paragraph , as failing to comply with the enablement requirement, because the Specification, while being enabling for "treating" certain specific types of cancer (breast cancer, prostate cancer, non-small-cell lung cancer, bladder cancer, colorectal cancer), does not reasonably provide enablement for inhibiting any type of cancerous tumor, as claimed.

Claim 12 recites:

> "12. A process for inhibiting a tumor in a patient comprising administering an effective amount of a compound as defined in claim 1 to said patient."

Claim 12 is a "method of use" claim that fails to comply with the enablement requirement of 35 U.S.C. 112, first paragraph, because it contains subject matter

which was not disclosed in the Specification so as to enable one skilled in the art to make and/or use the invention as claimed.

The applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Applying this rule to Claim 12, the scope of diseases claimed to be prevented or treated would thereby include all types and kinds of cancer, including such diverse types of cancer as leukemia, sarcoma, malignant lymphoma, as well as breast cancer, prostate cancer, lung cancer, pancreatic cancer, renal cancer, etc. However, the Specification only describes a few *in vitro* studies in human cancer cell lines, demonstrating concentrations of the claimed compounds of Formulae (1) and (Ia) needed to suppress 50% suppression of cell proliferation (IC_{50} values), please see the Specification, Tables on pages 52-53. Given the scope of the many types of cancer included within Claim 12, their varied etiologies, and the diversity of their patient populations, the disclosure in the Specification is insufficient to permit a person skilled in the art to practice "a method for inhibiting a tumor . . . by administering an effective amount of the compound as defined in claim 1 . . .." However, as described below, the Specification discloses sufficient support to enable "treating" or "inhibiting the growth of "certain *specific* types of cancerous tumor cells.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

Claim 13 is a "method of use" claim for inhibiting a tumor in a patient by administering an effective amount of the compound of claim 1to said patient.

The Breadth of Claims

The text of Claim 12 does not specify or enumerate those many types of cancer that would fall within its scope. As noted earlier, the applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." In view of this rule, Claim 12 may be reasonably interpreted to encompass all forms of cancerous tumors, as neither Claim 12 itself nor the Specification expressly defines a closed set of illnesses defined as cancer." Specifically, Claim 12 itself states only that the compounds are "for inhibiting a tumor" and therefore Claim 12 encompasses an open-ended set of types of cancerous tumors. The scope of Claim 12 reasonably encompasses such a broad spectrum of types of cancerous tumors that it is unreasonable to believe, on its face, that a particular chemical compound could be used "for inhibiting a tumor" of so many different types, in the absence of supporting

scientific data or references in the disclosure to the contrary. Due to the unpredictable nature of cancer and the fact that over 3,000 different cancers exist, the various types of cancers have different causative agents, involve different cellular mechanisms, and differ in treatment protocol, thus no single compound exists presently that is known to treat *all* cancers as a blanket therapeutic. Furthermore, the Merck® manual currently has many cancer treating agents (over 12,000 compounds), yet they are only known to treat one cancer each.

The State of the Prior Art

Claim 12 recites a method of use, "for inhibiting" such varied forms of cancerous tumors as breast cancer, lung cancer, prostate cancer, malignant melanoma malignant lymphoma, colorectal cancers, bladder cancer, and leukemia. However, subsequent to the time of this application, as stated above, no compound is known to treat *all* cancers or *all* tumors as a blanket therapeutic.

As stated in the Specification, page 3, Asciddemin possesses antiproliferative properties demonstrated on the model of mouse leukemia and described by F. Schmitz et al. (J. Org. Chem. 19917 56: 804-8), B. Lindsay et al. (Bioorg. Med. Chem. Lett. 1995; 5: 739-42) and J. Kobayashi et al. (Tetrahedron Lett. 1988; 29: 1177- 80) and in the model of human leukemia described by L. Bonnard et al. (Anti-cancer Drug Design 1995; 10: 333-46). In addition, 2-Bromoleptoclinidone shows cytotoxicity on the cellular model of leukemia. The cytotoxic properties were confirmed by F. Bracher (Pharmazie 1997; 52: 57-60) both *in vitro* on tumor cell lines in culture, and *in vivo* on models of human tumor cell lines (colon tumors SW-

620 and HTC116, renal tumor A498 and melanoma LOX IM VI) implanted into mice.

The Relative Skill of Those in the Art

Those practitioners who treat cancer of any type (medical clinicians, pharmacists and/or pharmaceutical chemists) presumably would be highly skilled in the art.

The Predictability or Unpredictability of the Art

Even though ascididemin compounds have been identified as having antiproliferative activity, as a practical matter their use as therapeutic agents for "inhibiting" cancerous tumors, or for treating a broad range of types of cancer, remains unpredictable. It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The court in In re Fisher, 427 F.2d 833, 839,. 166 USPQ 18, 24 (CCPA 1970) held that, "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." In other words, the more unpredictable an area the more specific enablement is needed in order to satisfy the statute. In the instant case, it has not yet been established in the art that antiproliferative activity would be effective, or even desirable, across the broad range of cancer types.

The nature of the pharmaceutical arts is such that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological

activities. There is no absolute predictability, even in view of the high level of skill in the art. This unpredictability is more pronounced where the diseases disclosed in the Specification are as complex and diverse in etiology and patient populations as the many different types of cancer disclosed in this application. As to "inhibition" of cancerous tumors by use of ascididemin-derived compounds, the examiner was not able to locate prospective clinical studies in the art demonstrating blanket "inhibition" of cancer, so there were no benchmarks against which to compare the efficacy of the claimed chemical compounds of Formulae (1) and (1a) for the absolute prevention of cancerous tumors, had the Specification done so. In light of the highly unpredictable nature of this art, the Specification failed to disclose facts which would enable the skilled artisan to use the compounds of Formulae (1) and (1a) to prevent or "inhibit" cancer without undue experimentation. On the other hand, use of ascididemin compounds to "treat" certain specific types of cancer, such as clinical studies of patients with colorectal cancerous tumors and melanomas, was already known and published in the art, greatly reducing the unpredictability for "treating" those types of cancer, or for "inhibiting the growth of" those types of cancerous tumors. In addition, the references in the Specification establish that levels of can be correlated with certain types of cancerous tumors (glioblastomas, astrocytomas, non-small-cell lung cancer, colorectal cancer, breast cancer, bladder cancer, and prostate cancer), which, when considered with the *in vitro* data using test compounds of Formulae (1) and (1a) showing inhibition of cell growth of the tumor cell lines also reduces the

unpredictability for "treating" those types of cancers or "inhibiting the growth" of those types of tumor cell lines.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

There appeared to be no working examples provided in the Specification where a compound of Formulae (1) or (1a) was administered to a mammal for "inhibition" of cancerous tumors of any kind claimed in Claim 12. However, the Specification and the Declaration under Rule 132 describe a few *in vitro* studies in human cancer cell lines, demonstrating concentrations of the claimed compounds of Formulae (1) and (Ia) needed to suppress 50% suppression of cell proliferation (IC_{50} values), please see the Specification, Tables on pages 52-53. The twelve human tumor cell lines used were obtained from the ATCC, and are glioblastomas, astrocytomas, non-small-cell lung cancer, colorectal cancer, breast cancer, bladder cancer, and prostate cancer.

The Quantity of Experimentation Necessary

When considering the claim of "inhibiting" the broad array of types of cancerous tumors in Claim 12 using compounds of Formulae (1) or (1a), in the context of the state of the art at the time of the invention, the absence of direction of working examples in the Specification, and the unpredictability of using the claimed invention for "inhibiting" cancer, someone skilled in the art would require an undue quantity of experimentation even to select which of the many compounds of Formulae (1) or (1a) would be useful to "inhibit" cancer, or to select those persons

(presumably both with or without cancer) who would benefit by administration of the claimed invention for "inhibiting" tumors, and the skilled artisan would have little assurance of success.

One skilled in the art would require an undue quantity of experimentation to make or use the invention for inhibiting all of the claimed types of cancerous tumors; however, it would not require an undue quantity of experimentation for the skilled artisan to use the invention for "inhibiting the growth of" certain types of cancer tumors, specifically breast cancer, prostate cancer, non-small-cell lung cancer, colorectal cancer, bladder cancer, as well as glioblastomas, and astrocytomas, with a reasonable likelihood of success. The Examiner recommends limiting the scope of claim 12 to encompass "a method of inhibiting the growth of a cancerous tumor in patient, wherein the cancer is selected from the group consisting of" and then insert the above-mentioned cancers or tumor cell lines.

Conclusion

6. In conclusion, claims 1-5 and 7-14 are pending, claim 12 stands rejected, and claims 1-5, 7-11, 13, and 14 appear allowable over the art of record.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571.272.8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Coppins
April 13, 2005

Joseph K. McKane
SPE, Art Unit 1626